Interventions to increase physical activity for people with congenital heart disease (Protocol)

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Interventions to increase physical activity for people with congenital heart disease

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of interventions to increase exercise and all types of physical activity, versus no intervention (exercise and physical activity as usual) for people with congenital heart disease.

BACKGROUND

Physical activity is increasingly recognized as an important modifying factor for physical fitness and health markers in people (Pate 2013). Physical activity is likewise essential for children and adults with congenital heart disease (ConHD) (Takken 2011; Tikkanen 2012; Duppen 2013; Longmuir 2013). Despite the growing body of literature on the benefits of physical activity, a large number of patients with ConHD do not adhere to recommendations (Reybrouck 2005; McCrindle 2007).

Physical activity refers to any bodily movements that result in an increase in energy expenditure above baseline resting energy expenditure (Caspersen 1985). Physical activity can be habitual and a part of daily living, as well as part of a structured exercise program. Physical exercise is defined as a subset of physical activity that is planned, structured and repetitive, and has as a final or an intermediate objective the maintenance or improvement of physical fitness (Caspersen 1985). Physical activity can be assessed by self-report or objective measures. However, physical activity is difficult to assess and interpret as no method is accurate. Interventions to increase physical activity are therefore also evaluated by health outcomes mediated by physical activity such as exercise capacity, health-related quality of life and risk markers for metabolic syndrome.

Children and adults with ConHD have reduced exercise capac-

ity across the different heart defects, in comparison with healthy people (Kempny 2012). The low level of physical activity in this population may explain this reduced exercise capacity, along with restrictions for unknown reasons (Lunt 2003; McCrindle 2007; Buys 2012a; Buys 2012b; Buys 2013).

The American Heart Association and the European Society of Cardiology recommend that children and adults with ConHD should be encouraged to be normally active and to participate in recreational sport activities (Takken 2011; Longmuir 2013). However, so far those recommendations are primarily based on expert opinion (Evidence level 5) rather than scientific evidence (Klausen 2012). The effects of interventions to increase physical activity in people with ConHD need to be further investigated and summarized.

Description of the condition

ConHD can be defined as "a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance" (Mitchell 1971). The reported birth prevalence worldwide has increased from 0.6 per 1000 live births in 1934 to 9.1 per 1000 live births after 1995 (van der Linde 2011). This corresponds to 1.35 million live births with ConHD each year, representing a major public health issue (van der Linde 2011). Before the end of the 1970s, less than 20% of children born with ConHD survived into adulthood (Warnes 2001). Today, 85% are expected to live until adulthood (Moons 2010). Their children are at increased risk of having a congenital abnormality (van der Bom 2011).The complexity of the disease varies and is reflected in survival rates, comorbidity and health-related quality of life (Warnes 2001). Genetic syndromes, gestational age and birth weight, as well as complications after surgery, add to comorbidity and contribute to the long-term outcomes (Wernovsky 2008).

Description of the intervention

Interventions can be facility based, home based or both. Promotion of and incentives to increase exercise and physical activity can be undertaken in a multitude of ways and situations. Exercise-based interventions for people with ConHD may take place at any relevant time from early childhood to adulthood. The type of intervention directed at people with ConHD should be adjusted to age, developmental stage and disease progression.

The first interventions for people with ConHD in the 1980s examined whether maximal oxygen uptake and exercise capacity could be safely improved by facility based exercise-based interventions (Goldberg 1981). As this seemed to be the case, it has been suggested that exercise-based interventions should become a part of the routine care of patients with ConHD (Tikkanen 2012; Duppen 2013).

Interventions to promote physical activity in children and adults have been encouraged and described (Hirth 2006; Baumgartner 2010; Takken 2011; Longmuir 2013). It is suggested that practitioners should promote physical activity in all medically-stable children and adults, according to the frequency and intensity recommended in general population guidelines. Moreover, sedentary time should be reduced, as prolonged sedentary time has been associated with negative health outcomes (Thorp 2011). Physical activity counselling should be based on a clinical assessment at every patient interaction. Social, cognitive and motivational theories should be used to guide a patient-centred approach, to identify personal relevant goals and develop an individual action plan (Longmuir 2013). The evidence for the recommendations is low (Evidence level 5), mainly based on expert opinion, as the body of knowledge is limited (Hirth 2006)

From research in other populations with cardiac disease, we know that exercise-based rehabilitation can lead to increased physical fitness, increased physical activity levels in daily life and a healthier lifestyle, which persist after termination of the exercise program (Vanhees 2012). Also, in individuals with ConHD, rehabilitation programmes can have persistent beneficial effects, although more evidence in this population is needed (Longmuir 1990; Rhodes 2005).

How the intervention might work

Physical activity behaviours are affected by personal, social and environmental factors (Heath 2012). Interventions that address personal factors to encourage physical activity involving education on health benefits, motivation and physical training are likely to be successful (Pate 2013). Education on health benefits and motivation can be improved by individually-tailored programmes based on behavioural and social cognitive theories (Kahn 2002).

Interventions mediated by behaviour change techniques, goal setting, feedback and problem-solving aimed at increasing daily physical activity levels, have proven successful in other fields (Olander 2013). Physical activity can be improved by clarifying the individual's specific needs, followed by individual or group-wise guidance to overcome barriers and foster motivation (Longmuir 2013). Goal setting, social support and behavioural reinforcement through self-reward and structured problem solving are examples of components of these types of interventions. Interventions involving behaviour change techniques can be described using a taxonomy in order to structure and specify the terminology used in invention studies (Michie 2011).

Self-efficacy is considered to be an important mediator in physical activity (Bar-Mor 2000; Olander 2013). Self-efficacy is defined as the belief that one has the ability to engage in a specific behaviour, such as physical activity (Bandura 1986).

There are convincing data demonstrating that contemporary cardiac rehabilitation programmes provide direct health benefits, reduce cardiovascular risk and event rates, increase healthy be-

haviours and promote active lifestyles (Kwan 2012). Furthermore there is evidence that a cardiac rehabilitation programme can improve quality of life in different populations with acquired heart disease (Weberg 2013). It is possible that exercise-based interventions could induce similar benefits in participants with ConHD.
There is a great interest in the association between exercise-based interventions and health-related quality of life. Health-related quality of life can be defined as the degree of overall life satisfaction that is positively or negatively influenced by an individual's perception of certain aspects of life that are important to them, including matters both related and unrelated to health (Moons 2004). Davies et al. have shown that exercise training that improves exercise capacity may have a clinically-important effect on health-related quality of life in people with mild to moderate heart failure (Davies 2010).The efficacy of physical activity for improving functional capacity and quality of life is clear in the short-term, but long-term effects are yet unknown (Piepoli 2013). It is unknown if exercise-based interventions can impact health-related quality of life in individuals with ConHD (Kovacs 2005). Studies have shown that self-assessed physical functioning poorly predicts actual exercise capacity in adolescents and adults with ConHD (Gratz 2009). Nevertheless, associations between physical fitness and different domains of health-related quality of life have been noted in some studies (Van De Bruaene 2011; Buys 2013). However, the way these dimensions interact and respond to exercise-based intervention programs is poorly understood.

Why it is important to do this review

Uncertainty exists as to whether exercise-based interventions are harmful or beneficial for people with congenital heart disease (ConHD), and whether current recommendations are effective. However, undue care/protection may be harmful if it restricts physical activity. By contrast, strenuous physical exercise may be harmful to individuals with ConHD due to their heart condition. There is a growing interest in the association between health-related quality of life and health-related fitness in people with ConHD. Trials have examined the effect of exercise training on physical fitness and health-related quality of life, but no consensus has been established (Duppen 2013). Thus, a systematic review of trials testing the interventions for increasing physical activity is needed to synthesize the evidence on quality of life, health-related fitness, cardiovascular risk factors and adverse events in people with ConHD.
This review aims to summarize the results of all randomized trials with an experimental intervention aiming to increase physical activity in individuals with ConHD. It is important to do this review, because it includes all interventions that intend to increase physical activity, and will not solely focus on exercise training. Habitual physical activities, such as increased leisure time activities and active transport, will also be included in the review.

OBJECTIVES

To assess the effects of interventions to increase exercise and all types of physical activity, versus no intervention (exercise and physical activity as usual) for people with congenital heart disease.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials, irrespective of publication status, blinding status or language.
We will only include unpublished trials if trial data and methodological descriptions are provided, either in written form or by direct contact with the authors.

Types of participants

All children (less than 18 years) and adults with congenital heart disease, whether or not they underwent surgical or catheter intervention, who are stable and allowed to be physically active.

Types of interventions

All exercise-based interventions, either alone or as a component of another intervention, with a duration of at least four weeks. We will include both counselling and education programmes, and structured exercise training programmes. We will also include interventions involving incentives for increased exercise and physical activity.
The intervention will be compared to exercise and physical activity as usual.
An example of counselling or educational programmes might be the encouragement to be physically active based on the theory of behavioural change, with encouragement provided either by group or individual therapy sessions or by innovative methods using internet or mobile phone applications. Examples of exercise training programs are: a supervised structured exercise training program in a cardiac rehabilitation centre, a home-based walking program supervised with GPS-based tele monitoring, or a non-supervised home-based exercise program in which patients choose their own physical activities.
We will include studies in which the exercise-based intervention is a component of another intervention, such as interventions to improve motor skills, increase lung function, adopt a healthier diet, quit smoking, or lose weight.
In both the intervention and control group, participants will receive usual medical care as defined by the study. Usual medical

care generally consists of regular follow-up in a tertiary care centre for congenital heart disease, drug treatment if necessary and the general advice to live healthily and to be normally active in daily life, sometimes with exercise restrictions depending on the type of underlying congenital heart defect (Takken 2011).

Types of outcome measures

Studies must report the first primary outcome in both intervention and control groups in order to be included.
We will extract outcomes at all time points and categorize them as: up to 6 months follow-up, 6 to 12 months follow-up and more than 12 months follow-up.

Primary outcomes

1. Health-related quality of life as measured by validated quality of life measures; determined by questionnaire, generic and/or disease-specific, reported as a continuous outcome.
2. Serious adverse events (SAE) during maximal follow-up. We have defined SAEs, according to the International Conference on Harmonisation Guidelines and the European Directive (European 2001), as "any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defects."

Secondary outcomes

1. Objective physical activity, determined by accelerometer, pedometer or heart rate, reported as a continuous outcome.
2. Self-reported physical activity and functioning, determined by a validated and standardized questionnaire, reported as a continuous outcome.
3. Exercise capacity: a) peak oxygen consumption Vo2 max or Vo2 peak; b) Watt max; c) V E/VCO_2-minute ventilation/ carbon dioxide production; d) oxygen uptake efficiency slope (OUES); e) oxygen consumption at ventilatory anaerobic threshold (AT), determined by cardio-pulmonary exercise test on treadmill or bicycle ergometer, reported as continuous outcomes.
4. Self-rated health determined by a validated and standardized questionnaire, reported as a continuous outcome.
5. Gross motor skills, determined by a validated test battery, reported as a continuous outcome.
6. Muscle function, determined by hand grip strength and upper leg muscle strength.

Search methods for identification of studies

Electronic searches

We will search the following databases from their inception: The Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*), MEDLINE (Ovid), EMBASE (Ovid), BIOSIS Citation Index (Thomson Reuters), Web of Science (Thomson Reuters), Latin American Caribbean Health Sciences Literature (LILACS via BIREME), the Chinese Biomedical Literature Database, advanced Google, and Cumulative Index to Nursing and Allied Health Literature (CINAHL via EBSCOhost).
We will use a systematic and sensitive search strategy to identify relevant randomized controlled trials without language or date restrictions. The preliminary search strategy for MEDLINE (Appendix 1) will be adapted for use in the other databases.
We will search for ongoing clinical trials and unpublished studies on the following clinical trial registers:

1. Current Controlled Trials;
2. ClinicalTrials.gov;
3. The WHO International Clinical Trial Registry Platform (ICTRP) on apps.who.int/trialsearch/.

Searching other resources

We will handsearch the reference list of relevant reviews, randomized and non-randomized studies, and editorials for additional studies. We will contact the main authors of studies and experts in this field to ask for any missed, unreported or ongoing trials.

Data collection and analysis

Selection of studies

We will provide a detailed description of our search results. Search results will be merged using reference management software, and duplicate records will be removed. Paired review authors (LLA and SHK; RB and SHK), with the lead author being part of all pairs, will independently assess titles and abstracts retrieved from the search in order to identify studies for eligibility and remove obviously irrelevant reports.. Full text of potential relevant reports will be retrieved. Multiple reports from the same study will be linked together. Full text reports will be examined for compliance with eligibility criteria. Correspondence with investigators will take place when appropriate to clarify study eligibility.The final selection will be undertaken by three authors (LLA, RB, SHK). In case of disagreements, decisions will be taken by discussion with an author who is not a content expert (JW). We will not be blinded to the author, institution, or the publication source of trials.

Data extraction and management

We will use a data extraction sheet in concordance with inclusion and exclusion criteria to extract and collect data. The data extraction sheet will be pilot tested. We will approach all corresponding

authors of the included trials for additional information relevant to the review's outcome measures and 'Risk of bias' components.

Assessment of risk of bias in included studies

The validity and design characteristics of each trial will be evaluated. We will use the 'Risk of bias' (ROB) table described in the *Cochrane Handbook*, section 8.5 (Higgins 2011) as a tool for assessing risk of bias in included studies. To draw conclusions about the overall risk of bias for an outcome it is necessary to evaluate the trials for major sources of bias, also defined as domains (random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias). We will perform separate sensitivity analyses for patient-reported outcomes (subjective outcomes) and for serious adverse events (Higgins 2011).

We will define the trials as having low risk of bias only if they adequately fulfil the criteria listed in the *Cochrane Handbook* (Section 8.5.a) and will perform summary assessments of the risk of bias for each important outcome (across domains) within and across studies. We will present a 'Risk of bias graph' and a 'Risk of bias summary figure' (Higgins 2011).

We will assess the risk of bias in the different domains as described in the *Cochrane Handbook* (Section 8.5.d; Higgins 2011). The judgement for each entry involves assessing the risk of bias as 'low risk', 'high risk', or as 'unclear risk', with the last category indicating either lack of information or uncertainty over the potential for bias. In case of significant bias effects in one or more bias domains, we will highlight the effect-estimate from trials with low or lower risk bias.

We will present results for all outcomes including adverse events in a 'Risk of bias summary figure'.

Measures of treatment effect

We will report continuous outcomes and the intervention effects as standardized mean differences (SMD) with 95% confidence intervals (CIs) (Higgins 2011).

We will report dichotomous outcomes as relative risks (RR) together with 95% CIs or, if rare, as Peto odds ratios (POR) with 95% CIs. We will report objective physical activity as a continuous outcome and the intervention effect as mean difference (MD) with 95% CIs.

Unit of analysis issues

We will include individualised randomized trials as well as cluster randomized trials. Unit of analysis issues in cluster trials will be dealth with as described in the *Cochrane Handbook* (Section 9.3). We will not include cross-over trials.

Dealing with missing data

We will contact all the first authors and contact persons of the trials that have missing data in order to request the relevant data. A modified intention-to-treat (ITT) analysis will be performed including, if possible, all randomized individuals who were tested at baseline or who did not withdraw their consent before the intervention.

In cases of missing data, for our primary outcomes we will use a 'complete-case analysis' by simply excluding all participants with the outcome missing from the analysis. Additionally, we will conduct sensitivity analyses for our primary outcomes by applying best and worst case scenarios.

Selective outcome reporting occurs when non-significant results are selectively withheld from publication (Chan 2004). We will explore selective outcome reporting by comparing publications with their protocols, if the latter are available.

Assessment of heterogeneity

The degree of heterogeneity observed in the results is quantified using diversity (D^2) (Wetterslev 2009) and inconsistency factor (I^2) statistics, which can be interpreted as the proportion of the total variation observed between the trials that is attributable to differences between trials rather than sampling error (chance) (Higgins 2002). $P \leq 0.10$ indicates significant heterogeneity, and the suggested I^2 statistic thresholds for low, moderate, and high heterogeneity are 25% to 49%, 50% to 74%, and $\geq$ 75% respectively (Higgins 2003). If $I^2 = 0$, we will report the results using the fixed-effect model only. In the case of $I^2 > 0$ we will report the results using both the random-effects and the fixed-effect models. However, we believe that there is little value in using a fixed-effect model in cases of substantial heterogeneity, which we suspect will be present in this review due to the inclusion of various patient types and outcome reporting. Consequently, we will emphasize the results from the random-effects model analysis unless a few trials dominate the meta-analysis (for example more than 50% of the cumulated fixed weight percentage). Additionally, in cases of $I^2 > 0$ (for the outcomes) we will seek to determine the cause of heterogeneity by performing meta-regression analyses using Comprehensive Meta-Analysis (CMA version one) and Stata version nine, and relevant subgroup and sensitivity analyses. We aim to combine trial results in a meta-analysis only when clinical heterogeneity is low to moderate. We will use the Chi^2 test to provide an indication of heterogeneity between studies, with $P \leq 0.10$ considered significant.

Assessment of reporting biases

Publication bias occurs when the publication of research results depends on their nature and direction (Dickersin 1990). We will examine this by creating funnel plots in order to detect either publication bias or a difference between smaller and larger studies

(small study effects), expressed as asymmetry of the funnel plot (Egger 1997).

Funding bias is defined as the biases in the design, outcome, and reporting of industry-sponsored research in order to show that an intervention has a favourable outcome (Bekelman 2003). Relationships between industry, scientific investigators and academic institutions are widespread and often result in conflicts of interest (Bekelman 2003). We may conduct a sensitivity analysis in order to examine the role of funding bias, if relevant (see Sensitivity analysis).

Data synthesis

We will use Review Manager software (RevMan 2012) to synthesize data, as well as TSA software version.0.9 (Thorlund 2011).

We will calculate the relative risk (RR) with 95% confidence intervals (CIs) for dichotomous variables (binary outcomes). We will also calculate the risk difference (Keus 2009). If the results are similar we will only report the RR. Additionally, we will calculate mean difference (MD) as the measure of absolute change with 95% CIs for continuous outcomes. If different scales for the same outcome are used in different trials, we will consider pooling the results using standardized mean difference (SMD) for continuous outcomes in order to combine common outcomes with different measures (e.g. exercise capacity and quality of life).

Adverse effects may be rare but serious, and hence important (Sutton 2002), when meta-analysis is applied for combining results from several trials that have binary outcomes (that is, event or no event). Firstly, we will apply the Peto odds ratio (POR) in the case of small event proportions. Most meta-analytic software packages do not include options for analyses to calculate RR when included trials have 'zero events' in both arms (intervention versus control). Exempting these trials from the calculation of RR and CI may lead to overestimation of a treatment effect, as the control event proportion may be overestimated. Thus we will perform a sensitivity analysis by applying empirical continuity corrections to our zero event trials as proposed by Sweeting et al (Sweeting 2004; Keus 2009), by applying an imaginary small mortality in both arms.

Trial sequential analysis (TSA)

Meta-analyses may result in type 1 errors due to sparse data and repeated significance testing when meta-analyses are updated with new trials (Wetterslev 2008; Brok 2009; Wetterslev 2009; Thorlund 2011). Systematic errors from trials at high risk of bias, outcome reporting bias, publication bias, early stopping for benefit and small trial bias may result in spurious P values.

In a single trial, interim analysis increases the risk of type 1 errors due to sparse data and repetitive statistical testing. To avoid type 1 errors, group sequential monitoring boundaries are applied to decide whether a trial could be terminated early because of a sufficiently small P value, that is, the cumulative Z curve crosses the monitoring boundary. Sequential monitoring boundaries can be applied to meta-analyses as well and are called trial sequential monitoring boundaries. In 'trial sequential analysis' (TSA) the addition of each trial in a cumulative meta-analysis is regarded as an interim meta-analysis and helps to decide whether additional trials are needed (Wetterslev 2008).

The idea in TSA is that if the cumulative Z curve crosses the boundary a sufficient level of evidence is reached and no further trials may be needed. However, there is insufficient evidence to reach a conclusion if the Z curve does not cross the boundary or does not surpass the required information size. To construct the trial sequential monitoring boundaries (TSMB) the required information size is needed and will be calculated as the least number of participants needed in a well-powered single trial (Brok 2008; Wetterslev 2008). We will adjust the required information size for heterogeneity with the diversity adjustment factor (Wetterslev 2009). We will apply TSA, since it prevents an increase of the risk of type 1 error (< 5%) due to potential multiple updating and testing on accumulating data, whenever new trial results are included in a cumulative meta-analysis. This provides us with important information in order to estimate the level of evidence on the experimental intervention (Pogue 1997; Pogue 1998; Thorlund 2009). Additionally, TSA provides important information regarding the need for additional trials and their required sample size (Wetterslev 2008; Wetterslev 2009). We will apply trial sequential monitoring boundaries according to a required information size estimated by a 10% difference in health-related quality of life at end of follow up. We will apply trial sequential monitoring boundaries according to an information size suggested by the trials at low risk of bias (Wetterslev 2008; Wetterslev 2009) and an a priori 20% relative risk reduction (RRR) of serious adverse events (SAEs) using a control event proportion suggested by large observational studies and by the pooled estimate of the event proportion in the included trial control groups. As SAEs seem rare in the trials conducted so far, and hence the ability to detect small intervention effects is low, we will also perform a TSA with an information size estimated based on an a priori 35% RRR of SAEs (Wetterslev 2009). We will also apply trial sequential monitoring boundaries according to a required information size estimated by a 10% difference in work capacity analysed by VO_2(ml/min), VCO_2(ml/min),VE (Pl/min), Watt max (watt) at end of follow up. We will use an anticipated Diversity of 25% to adjust the required information size and we will also use the Diversity actually measured from the included trials in the meta-analyses.

Subgroup analysis and investigation of heterogeneity

If possible we will conduct subgroup analysis based on type of exercise intervention, frequency (times per week), intensity, time (minutes per session), and type (strength training or cardiovascular training). We will report the authors' classifications of the

intensity of the exercise intervention as mild, moderate or vigorous. Furthermore, if possible, we will conduct subgroup analyses based on the different underlying heart defects (or groups of heart defects according to severity).

We will only make inferences from the subgroup analysis in terms of implications for clinical practice if the overall analysis of one of the co-primary outcomes becomes statistically significant. Where the analyses of the co-primary outcomes do not become statistically significant, we intend to reference them in 'Implications for research' to provide possible hypothesis generation for further research.

We will compare intervention effects in subgroups using a test of interaction (Altman 2003). We consider $P < 0.05$ to indicate significant interaction between the effect of increased physical activity on SAEs and health-related quality of life and the subgroup category 'frequency, intensity, time and type' (Higgins 2011).

We will explore the causes of moderate to high heterogeneity using meta-regression that includes the following covariates, if possible: mean age of the trial population at baseline; mean body mass index (BMI) of trial population at baseline; and proportion of individuals in each New York Heart Association (NYHA) class in the trial population at baseline.

Clinical relevance tables will be compiled for pooled outcome measures in additional tables to improve the readability of the review.

We will discuss minimal clinically important difference (MCID), defined as "the smallest change in QOL which individuals perceive as beneficial" (Thorlund 2011)..

Sensitivity analysis

As there is no sufficiently well-designed formal statistical method to combine the results of trials which are at high and low risk of bias, we will incorporate our 'Risk of bias' assessment by restricting meta-analyses to studies at low (or lower) risk of bias (Higgins 2011). Further sensitivity analysis, should there be sufficient trials, will take into account:

- a continuous correction of trials with zero events
- size of trial (e.g. comparing small and large trials)
- data from trials only published in abstracts compared to those in published papers
- industry versus public funding of trials

We will calculate RR with 95% CI applying complete case analysis, if possible, for the sensitivity and subgroup analyses based on SAEs and health-related quality of life outcomes.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

1. exp Exercise/
2. Physical Fitness/
3. exp Sports/
4. Rehabilitation/
5. Dance Therapy/
6. exp Exercise Therapy/
7. Recreation Therapy/
8. Physical Exertion/
9. exp "Physical Education and Training"/
10. Dancing/
11. exercis*.tw.
12. aerobic$.tw.
13. sport$.tw.
14. walk$.tw.

15. bicycle$.tw.
16. ((lifestyle or life-style) adj5 activ$).tw.
17. ((lifestyle or life-style) adj5 physical$).tw.
18. (physical$ adj5 (fit$ or train$ or activ$ or endur$ or exert$ or perform* or inact*)).tw.
19. anaerobic.tw.
20. rehabilitat$.tw.
21. heart rate recovery.tw.
22. danc*.tw.
23. (run* or jog*).tw.
24. or/1-23
25. exp Heart Defects, Congenital/
26. exp Heart Diseases/cn [Congenital]
27. (heart adj2 (defect* or abnormal* or malform*)).tw.
28. (congenital adj2 (heart or cardiac or cardio*)).tw.
29. or/25-28
30. 24 and 29
31. randomised controlled trial.pt.
32. controlled clinical trial.pt.
33. randomized.ab.
34. placebo.ab.
35. drug therapy.fs.
36. randomly.ab.
37. trial.ab.
38. groups.ab.
39. 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40. exp animals/ not humans.sh.
41. 39 not 40
42. 30 and 41

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DECLARATIONS OF INTEREST

None known.